Osteosarcoma, Fibrous Dysplasia, and a Chromosomal Abnormality in a 3-Year-Old Child

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Osteosarcoma is a type of malignant bone tumor that is rare among children less than five years old. This report describes a 3-year-old boy with osteosarcoma of the right proximal femur and polyostotic fibrous dysplasia of the right femur and tibia. After hemipelvectomy, histologic examination of the amputated limb disclosed that the osteosarcoma had developed in a focus of fibrous dysplasia. Cytogenetic analysis of the patient's blood lymphocytes revealed a 4q−/7p+ translocation in all cells. The patient's mother had an identical translocation but did not have a history of osteosarcoma or evidence of fibrous dysplasia. The chromosomal abnormality and the developmental osseous disorder may have predisposed this patient to developing osteosarcoma at an exceptionally young age.

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OSTEOSARCOMA IS A TYPE of malignant bone tumor that occurs mainly in the second and third decades of life and rarely in children less than 5 years old.[9,15] It occurs more frequently in patients with certain disorders of bone, such as Paget's disease and fibrous dysplasia. Osteosarcoma also occurs in 1–2% of patients who have had the hereditary form of retinoblastoma.[4,11] In these patients, it occurs at sites both within and distant from the field of radiation but it also develops in those who have not had radiation or chemotherapy. Furthermore, reports of several affected relatives in a family suggest that a proportion of the cases of osteosarcoma are hereditary,[6] and osteosarcoma is also associated with brain tumors and soft-tissue sarcomas in certain cancer families.[1,14] However, there have been no reports of specific chromosomal abnormalities associated with an increased incidence of osteosarcoma. In this report, we described a 3-year-old child with polyostotic fibrous dysplasia in whom osteosarcoma developed. He also had a 4q−/7p+ chromosome translocation in all of his blood lymphocytes. The chromosomal abnormality and the fibrous dysplasia may have led to the early onset of osteosarcoma.

Case Report

The patient, a 3-year-old white boy, was referred to St. Jude Children's Research Hospital (SJCRH) for evaluation and treatment of a bone tumor. He had been limping intermittently for the previous 11 months and was taken to a physician after a progressive worsening of symptoms. A radiograph of his hip showed a bone lesion in the right proximal femur. Open biopsy examination revealed a malignant bone tumor, so the patient was referred to SJCRH for further evaluation. He had not previously received diagnostic or therapeutic radiation, and there was no family history of retinoblastoma, bone tumor, or any other form of cancer. The mother had had one spontaneous abortion of a 4-month-old fetus after a fall.

On admission to SJCRH, he appeared to be a healthy 3-year-old in no acute distress; the only abnormal physical finding was pain and limitation of movement of the right hip. Results of laboratory studies were within normal limits. On skeletal survey, only the lesion in the right proximal femur was found (Fig. 1). Several other lesions in the right femur were detected by means of ^{99m}Tc-diphosphate bone scan (Fig. 2), but all evidence of gross disease was apparently confined to the right leg. Examination of the open biopsy specimen (obtained previously) confirmed a diagnosis of osteosarcoma, so a right hemipelvectomy was done. Histologic examination of the amputated limb disclosed several areas of fibrous dysplasia in the right femur and proximal tibia, and indicated that the osteosarcoma had arisen in a focus of fibrous dysplasia (Figs. 3 and 4).

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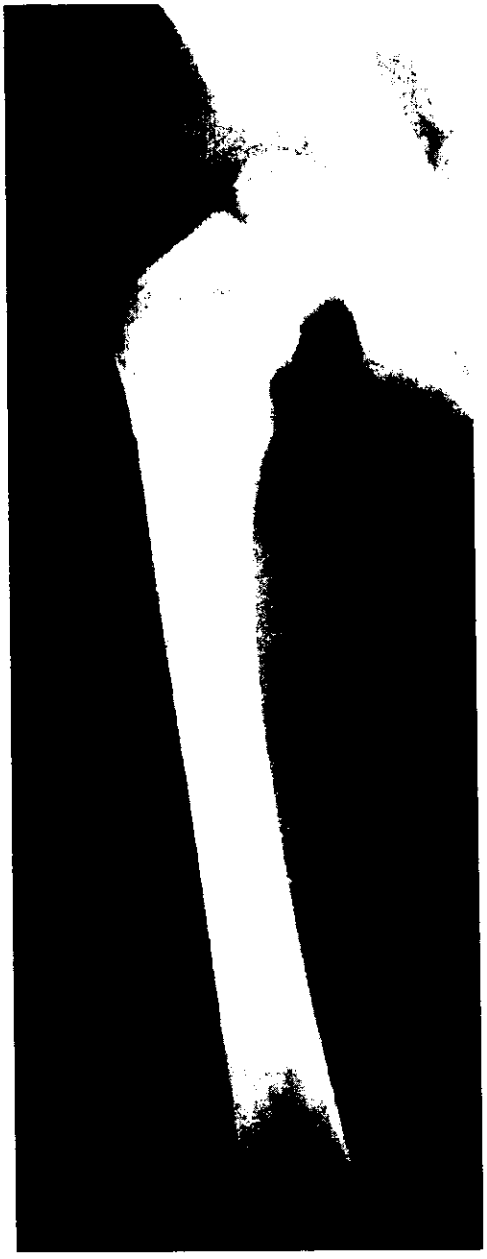

FIG. 1. Radiograph of right femur showing an osteolytic bone lesion in the right proximal femur with periosteal reaction.

An inherited genetic abnormality was suspected because the osteosarcoma had developed in such an exceptionally young patient. Banded karyotypes were prepared by means of standard techniques[10-13] using blood lymphocytes obtained from the patient prior to therapy and from all immediate family members.[10-13] Analysis of the patient's karyotype identified a 4q−/7p+ translocation in all cells without any apparent loss of genetic material (Figs. 5 and 6). The precise description of the karyotype is: 46,XY,del(4)(pter → q27::t(4;7)(7p22::4q28 → 4q35). Karyotype analysis of the blood lymphocytes from immediate family members revealed that the mother (27 years old) had the same translocation, and that the father (30 years old) and the patient's 2-year-old sister had normal karyotypes.

The patient was admitted to an adjuvant chemotherapy protocol and received methotrexate (2500 mg/m²) with leucovorin rescue on days 1–3, followed by adriamycin (50 mg/m²) plus cyclophosphamide (600 mg/m²) on day 15. These drugs were given in five-week cycles for a period of 50 weeks. Administration of adriamycin was discontinued after a total dosage of 350 mg/m² was reached. The treatment was tolerated well, and the child has remained free of disease and is now off therapy.

Discussion

The role of genetics in the development of childhood cancers has become increasingly apparent. As more patients survive malignant disease, it will be

FIG. 2. ^{99m}Tc-diphosphate bone scan showing increased uptake in the right proximal femur as well as in the lower femur and proximal tibia.

important to identify those who are inherently at higher risk for the development of second cancers, and whose offspring are at greater risk for the development of the primary malignant disease. Knudson has proposed a two-mutation model to account for the occurrence of hereditary forms of childhood cancer.[5] Six criteria have been suggested for distinguishing individuals with hereditary forms of cancer: 1) occurrence at an earlier age then expected; 2) associated pathologic abnormalities of the target tissue; 3) specific chromosomal abnormalities; 4) occurrence of multiple primary tumors; 5) associated congenital abnormalities; and 6) family history of the same or associated tumors.[14]

Our patient met the first three criteria, including a specific chromosomal abnormality, i.e., the 4q−/7p+ translocation. There have been only 2 reported cases documenting an association between somatic chromosomal abnormalities and an early onset of osteosarcoma; both involved fairly well described cytogenetic abnormalities not known to increase the risk of bone cancer. One patient had trisomy 21 (Down's syndrome) and the osteosarcoma developed when he was nearly 5 years old.[16] The other had congenital adrenal hyperplasia and a 47,XYY karyotype, and osteosarcoma developed when he was 9 years old.[18] Although he was younger than most patients with this tumor, his bone age was actually 13 years—well within the peak-age range for the onset of osteosarcoma.

The fibrous dysplasia in our patient may have played a role in the development of osteosarcoma, since this disorder is associated with an unusually high incidence of malignant bone tumors.[2,7] Such tumors almost always occur in a focus of fibrous dysplasia, suggesting malignant transformation of the developmentally abnormal tissue.[12] However, the average age at which patients with fibrous dysplasia develop osteosarcoma is the same as that for the general population, and the youngest patient previously reported was 8 years old.[3,12] That osteosarcoma develops in these patients more frequently but not at an earlier age may be due to an increase in the number of cells at risk for malignant transformation. This would also explain the higher frequency of osteosarcoma in patients with the polyostotic as compared to the monostotic form of the disease.

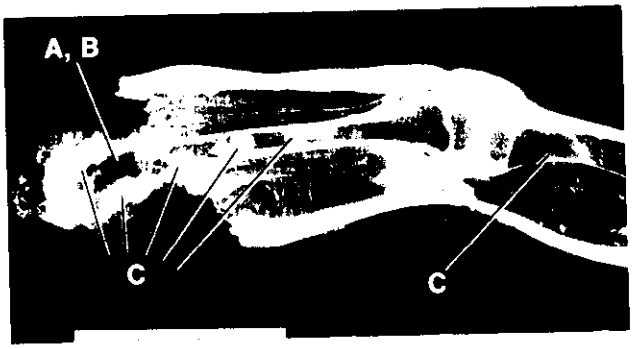

FIG. 3. The amputated right lower limb was 47 cm long. A small portion of the acetabulum was included in the resection, and the proximal surgical margin was free of gross and microscopic tumor. A sagittal section of the limb showed foci of whitish tissue in the medullary cavity of the proximal tibia and several portions of the femur. These areas corresponded to areas of increased uptake on the ^{99m}Tc diphosphate bone scan (see Fig. 2). Letters refer to corresponding histologic descriptions in Fig. 4.

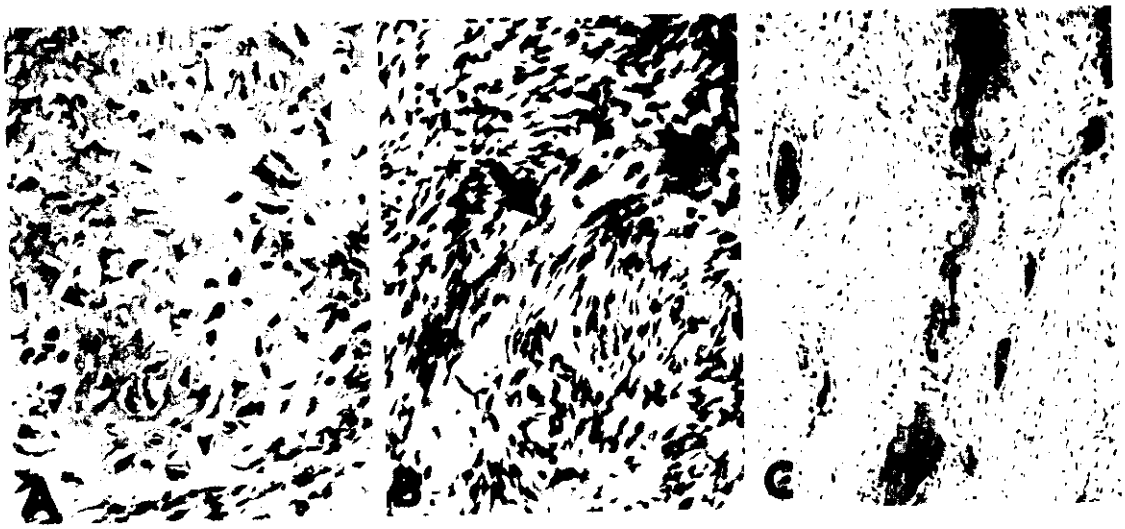

FIG. 4A. Photomicrograph of the portion of the proximal femur that had been biopsied. It was hemorrhagic and contained residual osteosarcoma tissue, composed of large hyperchromatic cells that had formed osteoid (H & E, ×104). B. Photomicrograph of the immediate surrounding areas which contained densely packed, malignant fibrous stroma that also formed osteoid (arrow) (H & E, ×140). C. The majority of this lesion and all other lesions in the femur and tibia consisted, as shown in this photomicrograph, of loose fibrous stroma and irregular trabeculae of immature bone, characteristic of fibrous dysplasia (H & E, ×70).

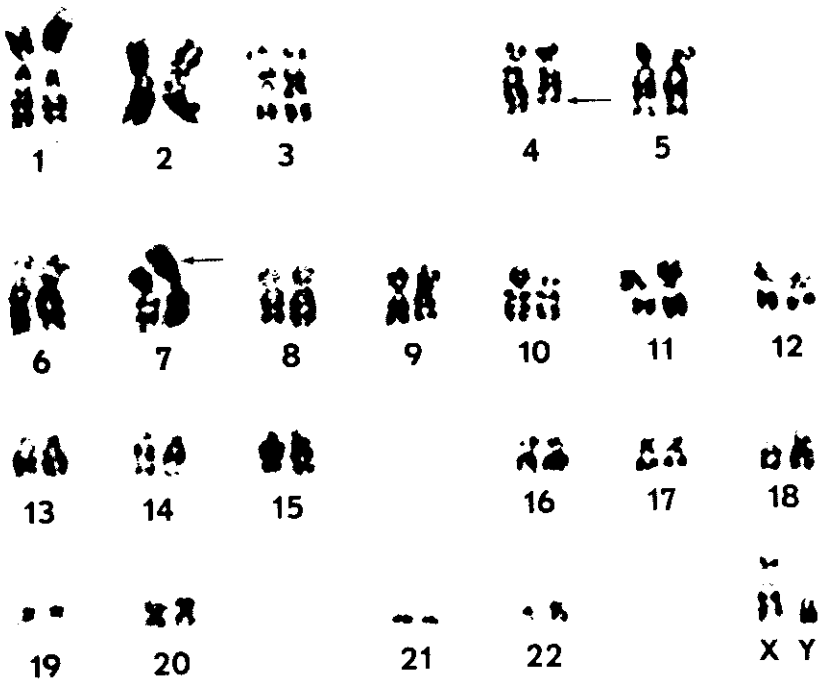

FIG. 5. A translocation between chromosomes 4 and 7 was identified from analysis of banded karyotype of this patient's blood lymphocytes. The precise description is: 46,XY,del(4)(pter → q27::),t(4;7)(7p22::4q28 → 4q35).

The same factors which usually cause osteosarcoma could be responsible for the development of this tumor in patients with fibrous dysplasia. However, when the onset of osteosarcoma is very early, additional contributing factors should be suspected.

It is less likely that the chromosome translocation is responsible for the fibrous dysplasia, since this disease is rarely hereditary. However, it is probable that the 4q−/7p+ translocation in our patient predisposed him to the development of osteosarcoma at an exceptionally early age. Although a mutation of either chromosome could have led to malignant transformation of the target tissue, the long arm of chromosome 4 is more strongly implicated. In contrast to chromosome 7 which was essentially intact, the distal portion of the long arm of chromosome 4 was

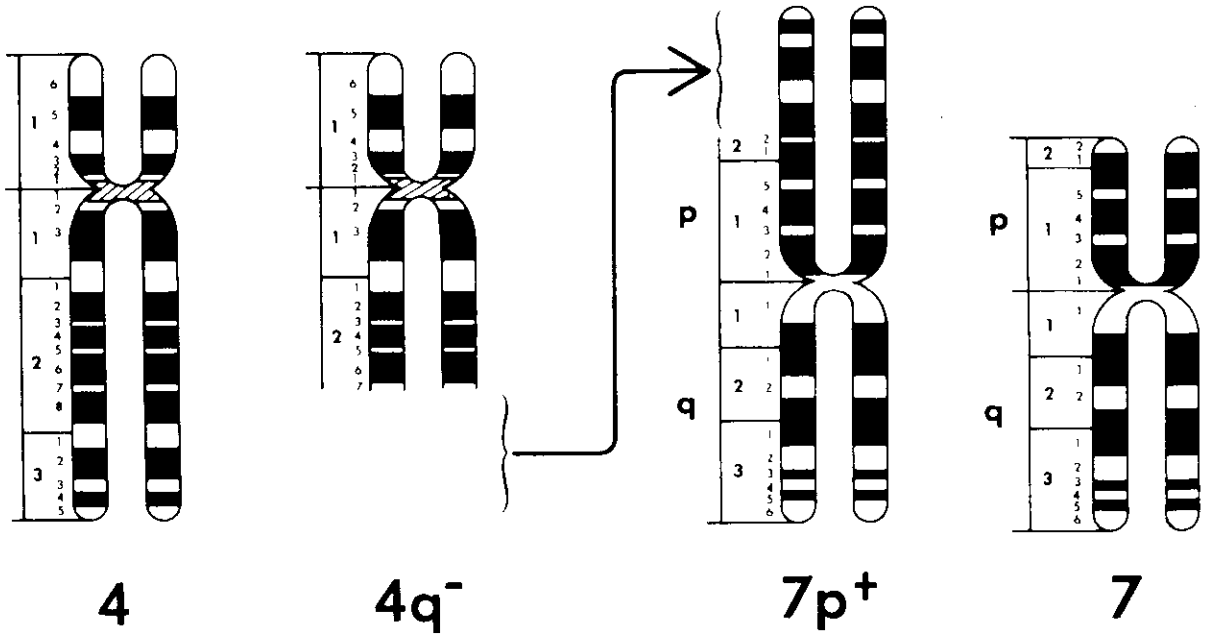

FIG. 6. Diagram representing the chromosome 4 and 7 pairs and the breakpoints of the chromosomes involved in the translocation.

translocated and may not have normal transcriptional activity. The absence of osteosarcoma in the mother, who had the same chromosomal abnormality, may be explained by means of a two-mutation model. In this case, the alteration of either chromosome 4 or 7 could be the first of two (or more) genetic mutations necessary for malignant transformation, and the development of osteosarcoma would depend on the likelihood of the second mutation. Moreover, she may still be at risk for developing osteosarcoma. While this point remains speculative, this child is probably at high risk for developing subsequent malignant diseases, and this predisposition may be influenced by the treatment with chemotherapeutic agents. Furthermore, if he survives to have a family in later years, a fourth of his offspring should inherit the same translocation and therefore be at increased risk of developing cancer.

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